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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,764	09/27/2000	Joseph R. Pisegna	M-8978 US	7433

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 02/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,764	PISEGNA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,20-29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-10,20-29,31 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on August 15, 2005 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-4, 6-10, 20-29 and 31-32 are pending.

Applicants' amendment filed August 15, 2005 is acknowledged, and applicants' response has been fully considered. New claim 32 has been added. Therefore, claims 1-4, 6-10, 20-29 and 31-32 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Previous rejection of claims 1-4, 6-10, 20-29 and 31 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is maintained, and claim 32 has been added to the rejection.

The specification is not enabling for a method of increasing the efficacy of a gastric H^+/K^+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin or a gastrin analog in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing a pentagastrin, a gastrin or a gastrin analog because the specification only discloses cursory conclusions without data

supporting the findings, which state that the present invention provides a method of treating pathological conditions characterized by excess gastric acid secretion, in particular the method of administering a gastrin, a pentagastrin or an analog thereof in conjunction with a PPI, which will result in increased efficacy, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI and a container containing pentagastrin (page 2, line 7-page 4, line 2). However, there are no indicia that the present application enables the full scope of the claim in view of a method of increasing the efficacy of a PPI in a human in need of PPI treatment and a kit for the treatment of pathology of excess gastric acid secretion as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding analogs of gastrin or pentagastrin, and PPIs, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for administering pantoprazole to healthy humans having pentagastrin (1

μg/kg/hr) -induced gastric acid secretion and monitoring the effect of pantoprazole in the inhibition of pentagastrin-induced gastric acid secretion (Example 1).

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Simon *et al.* , Aliment. Pharmacol. Therap. 4, 239-245 (1990)) indicates the effect of a PPI, BY1023/SK&F 96022 on the pentagastrin-stimulated acid secretion in healthy male volunteers; Murphy *et al.* (U. S. Patent 4,997,950) teach the use of analogs from C-terminus of gastrin in adjunctive therapy with a PPI, omerprazole in animal models. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin or a gastrin analog in conjunction with a PPI, and the effect of the gastrin or pentagastrin peptide in increasing the efficacy of the PPI in a human in need of a PPI treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of increasing the efficacy of a PPI in a human in need of a PPI by administering an effective amount of a gastrin peptide in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin peptide, however, the in vivo effects of using an effective amount (e.g., 0.1-10 mg/kg/hr) of gastrin, pentagastrin or a gastrin analog to increase the efficacy of a PPI in a human in need of PPI treatment are not adequately described or demonstrated in the specification. For example, the specification only describes pentagastrin is an agent that is typically to increase acid secretion (page 2, lines 9-10), and PPIs are potent inhibitors of gastric acid secretion by inhibiting H^+/K^+-ATPase (page 2, lines 1-5); and Example 1 indicates pentagastrin (1 μg/kg/hr, not in the range of

0.1-10 mg/kg/hr) is administered continuously to induce hypersecretion in healthy subjects, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, the specification has not demonstrated an effective amount of pentagastrin such as 0.1-10 mg/kg/hr can increase the efficacy of PPI in inhibiting gastric acid secretion in a human in need of PPI treatment as compared to the efficacy of using PPI alone, and there is no reference point for comparison. Since pentagastrin can also induce gastric acid secretion other than increasing the efficacy of PPI, the effect of pentagastrin in combination with a PPI in the treatment of excess gastric acid secretion in a human in need of PPI treatment is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of increasing the efficacy of a PPI in mammal by administering a gastrin, a pentagastrin, or an analog of gastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and gastrin, or an analog of gastrin or pentagastrin. The specification indicates the pentagastrin can be administered before, simultaneously with or after the PPI administration with the general dosages (0.1-10 mg/kg/hr) for pentagastrin, gastrin, or analogs thereof (page 2), and Example 1 demonstrates single doses of *i.v.* pantoprazole ranging 20-120 mg suppressed gastric acid secretion in a dose-dependent manner in healthy subjects under continuous pentagastrin (1 μg/kg/hr) -induced hypersecretion. However, the specification has not demonstrated an effective amount (0.1-10 mg/kg/hr) of a gastrin, a pentagastrin, or an analog of gastrin increases the efficacy of a PPI in a human in need of PPI treatment as compared to the efficacy of PPI using

alone. Moreover, there are no working examples indicating the effects of gastrin, pentagastrin, or an analog thereof in increasing the efficacy of various PPIs in a human in need of PPI treatment. Because pentagastrin has also an effect of inducing gastric acid secretion other than increasing efficacy of PPI, it is unpredictable about the effect of pentagastrin on gastric acid secretion in combination therapy. Since the specification does not provide sufficient teachings on the use of gastrin, pentagastrin or various analogs thereof in conjunction with a PPI, and the in vivo effects of these peptides in increasing efficacy of PPI and inducing gastric acid secretion in a human in need of PPI treatment, it is necessary to carry out undue experimentation to assess the effects of gastrin, pentagastrin or various analogs thereof in the claimed method.

(6). Nature of the Invention

The scope of the claims encompasses a method of increasing the efficacy of a PPI in a human in need of a PPI by administering a gastrin, a pentagastrin or an analog thereof in conjunction with the PPI, but the specification has not provide sufficient teachings, nor has demonstrated using an effective amount of the peptide in conjunction with a PPI in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods, the effect of the variant is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to assess the effects of using a gastrin, a pentagastrin or various gastrin analogs in the method of increasing efficacy of various PPIs in a human in need of PPI treatment.

Response to Arguments

Applicant indicates they have provided objective evidence that pentagastrin increases the efficacy of a typical PPI as stated in the previous response, and the reference by Bardan et al. (2004) Supplement to Gastroenterology, 12(4): Suppl. 2, Abstract M1439, which indicates that prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion. This effect is mediated by a local effect of PG. Co-administraton of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole. Thus, this published scientific literature thus clearly teaches prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion, while the pending claims are drawn to a method of increasing the efficacy of a gastric H+/K+-ATPase pump inhibitor (PP1) in a human in need of a PPI by administering a PPI in conjunction with pentagastrin, gastlin or a gastrin analogue. Moreover, it is noted that claim 32 is drawn to the use of pentaeastrin in conjunction with omeprazole, precisely the combination described in the cited reference. With respect to the use of gastrin or gastrin analogues instead of pentagastrin, or the use of PPIs other than omeprazole, the Examiner has failed to offer any objective evidence that would lead one of skill to conclude that gastrin or gastrin analogues would function differently than pentagastrin, or, other PPIs would function differently than omeprazole in the presently claimed method. With respect to the fact that the abstract pertains to testing in rats, applicants indicate that data from in vitro or animal testing is generally sufficient to support therapeutic utility, see M.P.E.P. 2107.02(c). Therefore, applicants have provided objective experimental evidence establishing the efficacy of the presently claimed method (pages 5-7 of the response).

The response has been fully considered, however, the argument is not found persuasive because the specification merely demonstrates continuous administration of pentagastrin at 1 μg/kg/hr induces hypersecretion in healthy subjects, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, the specification has not demonstrated the administration of an effective amount (e.g., 0.1-10 mg/kg/hr) of a gastrin peptide increases the efficacy of a PPI in a human in need of PPI treatment. Because of insufficient teachings in the specification and analysis of other In re Wands factors (see above), it is necessary to carry out undue experimentation to assess the effect of a gastrin peptide on efficacy of a PPI on acid secretion in the claimed method. Furthermore, Bardan et al. (2004) is a post filing reference, the content of the reference cannot be used as the omitted description for the specification at the time of filing of the instant application. Examiner does not dispute that the in vitro data and animal model are sufficient to establish the therapeutic utility for a compound when the correlation exists between the in vitro data and in vivo test, however, the claimed method is directed to a method of increasing efficacy of a PPI in a human subject in need of PPI treatment, which is not directly correlated to the rat model indicated in Bardan et al. Moreover, Bardan et al. (2004) indicate co-administration of pentagastrin and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole, which also suggests undue experimentation is needed to assess the effect of pentagastrin in potentiating omeprazole in the clinical treatment. Thus, the enablement rejection is maintained. Please call Examiner to set up a telephone interview to discuss the issue.

New Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 has the same scope as claim 24, since claim 31 recites the limitations of "said one or more agents is pentagastrin" and "said PPI is dehydrated".

Conclusion

4. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
Patent Examiner

CHIH-MIN KAM
PATENT EXAMINER

CMK
January 31, 2006